Enantioselective Aza-Diels Alder reaction catalyzed by clay supported Schiff base complex[1]

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[1] Taken in part from the Ph D Thesis of V. Kannan

Abstract

Clay supported catalysts based on 2- hydroxy naphthaldehyde and amino acids, their copper and titanium complexes have been described. The catalysts were found to be active towards the synthesis of pyrano-, furanoquinolines through Aza-Diels Alder reaction. The catalysts gave good yield and high enantioselectivity. The catalysts were environmentally friendly, economical, synthetically robust and reusable.

Keywords: Peptide metal complex, Clay, Aza-Diels Alder reaction, enantioselective reaction

1. Introduction

Optically active compounds play an important role in several areas of organic and biological chemistry.[1] Several organic reactions in homogeneous as well as heterogeneous phases were found to be catalyzed by a wide variety of Schiff's base complexes. Synthesis of biologically active molecules has been effectively carried out using Aza Diels Alder reaction[2]. Chiral metal complexes have been widely used as catalysts for Aza Diels Alder reaction [3-5]. They are used for the synthesis of heterocyclic compounds containing six membered rings. Organic reactions utilizing α-amino acids as chiral source are more prevalent in asymmetric synthesis [6-8]. Peptides have been found useful as asymmetric catalysts and templates for the controlled formation of Ag nanoparticles [9]. Nevertheless, Schiff base metal complexes of peptides were scarcely used in asymmetric synthesis due to complexity in structure and difficulty in preparation [10]. Hydrocyanation reaction has been was reported to be catalyzed by a titanium (IV)- peptide complex in the homogeneous medium[11,12]. Schiff base Zn (II) complex derived asymmetric ligands were reported [13]. We are articulating the idea of anchoring a peptide - metal complex on a readily available and economical support like clay.

Normally, it is a difficult task to develop a new chiral catalyst which exhibits Lewis acid property which can be used for C-C bond formation [14]. Several bioactive compounds of the alkaloid family were synthesized by reactions catalyzed by imines[15]. The synthesis of such compounds take place through a three-component reaction mode utilizing aldehydes, amines and dihydropyran/ dihydrofuran. Aza Diels Alder reaction offers a simple one step method for the synthesis of six membered heterocycles [16,17]. Several catalysts including transition metal complexes [18], chiral Lewis acids of Lanthanide elements [19] and polyaniline–p-toluenesulfonate salts [20] have been reported. But, clay supported catalysts for asymmetric reactions are very few in numbers [21-23]. In our effort to produce cheap supported catalysts[24-25], we have selected K10 montmorillonite clay as the support. The present manuscript deals with the synthesis of various furano [3, 2, c] and pyrano [3, 2, c] quinolines through Aza-Diels Alder reaction catalyzed by clay supported dipeptide- Schiff's base metal complexes.

2. Experimental

2.1. Materials and Methods

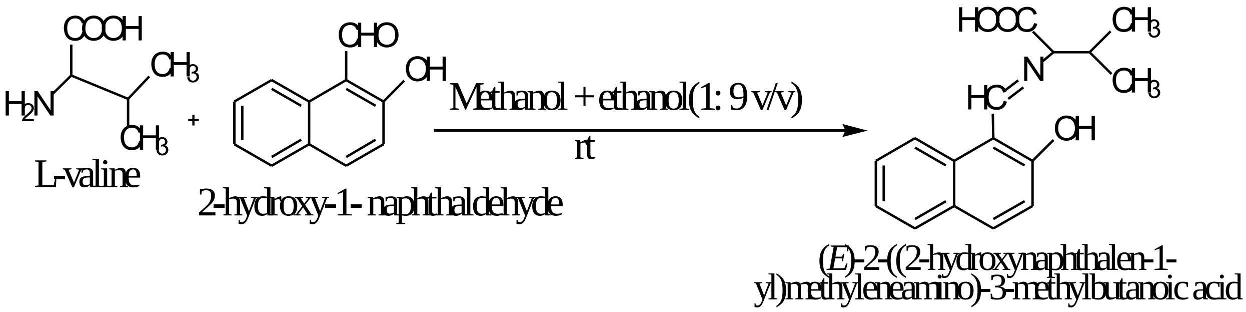
Analytical grade reagents and solvents were used. ^{1}HNMR spectra were recorded on Varian INOVA-400MHz instrument in $CDCl_3$. IR spectra were obtained from Jasco 4100 FTIR instrument. Column chromatography was carried out using silica gel (60-120 mesh), which was supplied by (Merck India Ltd). Reactions were monitored using Thin Layer Chromatography, which was carried out using pre-coated silica gel plates (Merck 60F-254). Melting points were determined using the capillary tube method with an electrothermal apparatus. HPLC analyses were carried out using Shimadzu *i* Series Prominence 20A. HPLC or ^{1}HNMR was used to determine diastereomeric ratio and HPLC with chiral column (OJ-H) was used to determine enantiomeric excess. Thermal stability of the catalysts were determined using Pyris 6 Diamond model Perkin Elmer instrument under a flow of dry Nitrogen. The temperature range was from 30^{o}C to 1000°C. The heating rate was 10°C/ min. Varian, Cary 5000 spectrophotometer was used to record Diffuse Reflectance UV-Vis spectra.

The detailed experimental procedures are given as Supplementary information.

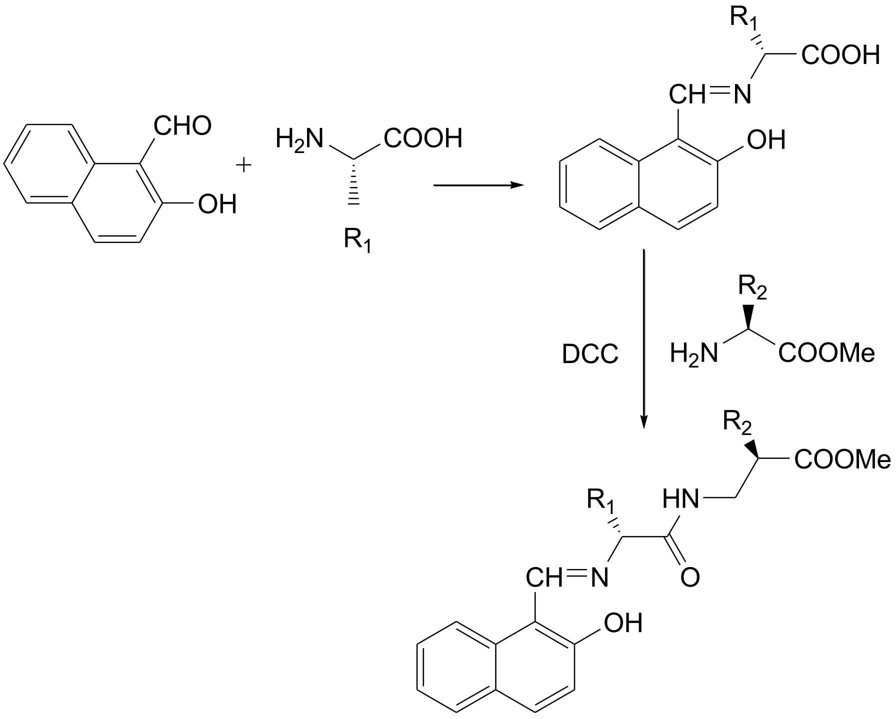
3. Results and discussion

3.1. Prepartion of the dipeptide ligand

Dipeptide ligands [Scheme 2] were prepared by adopting a procedure reported earlier with slight modification [11] by protecting the amino end of one amino acid by Schiff base formation using 2-hydroxy-1-naphthaldehyde (Scheme 1) and protecting the acid end of the second amino acid by ester formation.



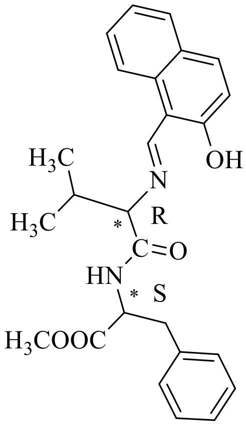
Scheme 1. Synthesis of amino acid - naphthaldehyde Schiff base



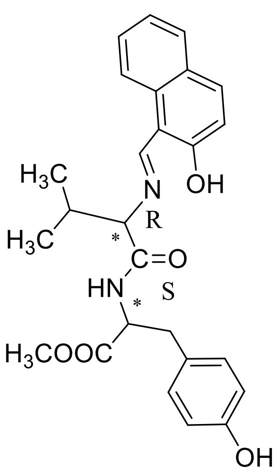
Scheme 2. General scheme of the synthesis of dipeptide type ligands.

3.2. Preparation of dipeptide metal complexes

Dipeptide metal complexes were prepared by reacting the dipeptide (Fig 1) and metal salts in the ratio 1:1 at room temperature using dichloromethane as solvent under N_2 atmosphere (Fig 2). The copper complexes were green in colour and titanium complexes were yellow. The prepared metal complexes were characterized using FT-IR spectra, UV-Visible spectra etc.



DP 2

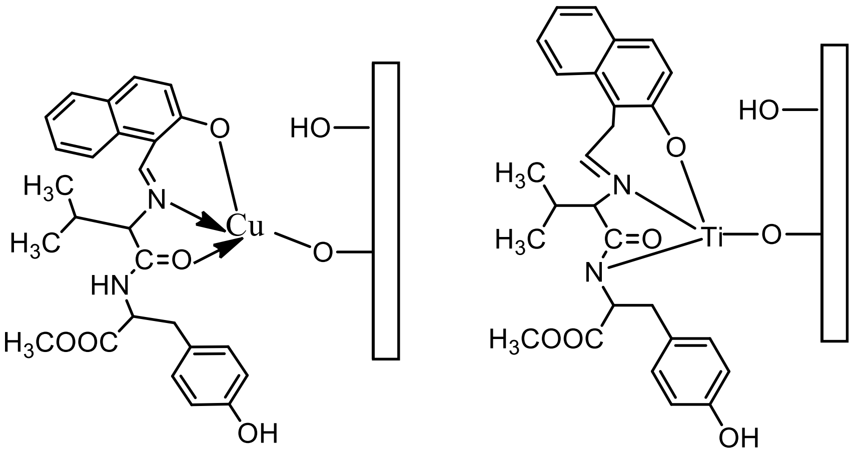


DP 3

Fig 1. Structures of the dipeptides

3.3. Preparation of K10 clay supported peptide catalyst [26]

The peptide metal complexes were supported on activated K10 clay. The clay was ion exchanged with sodium. The sodium exchanged clay was reacted with the peptide metal complexes and form clay supported catalysts (Scheme 3)



Scheme 3. Proposed structures of the clay supported metal complexes

3.3. FT-IR and UV-Vis spectra of the complexes [26]

"FT- IR spectra of the free ligands and the complexes exhibited a broad band in the region 3300-3400cm^{-1}, which can be attributed to the stretching vibration of the OH group. The C=N imine stretching vibration was observed in the region 1619-1655 cm^{-1} for the free ligand, clearly indicating the formation of Schiff bases. When the spectra of the complexes were compared with those of the free Schiff base ligands, the υ(C=N) band observed at 1650cm^{-1} was shifted to a lower frequency (1620cm^{-1}), indicating that the imino nitrogen has coordinated to the metal ion. The negative shift of 30 cm^{-1} for the band indicated weakening of the C-N bond.[27]"

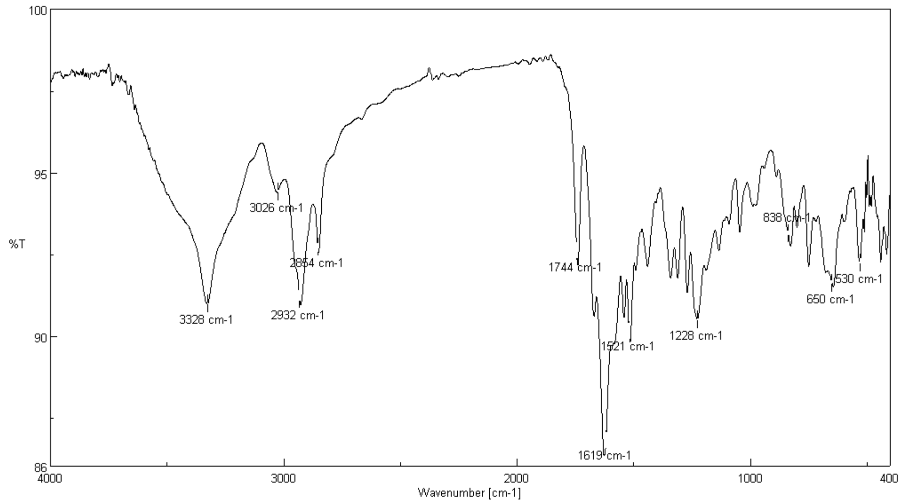


Fig 2a

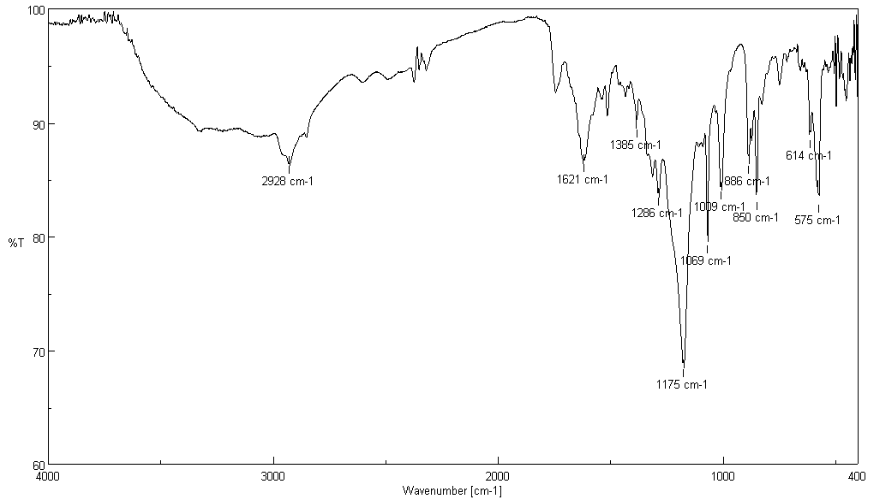


Fig 2b

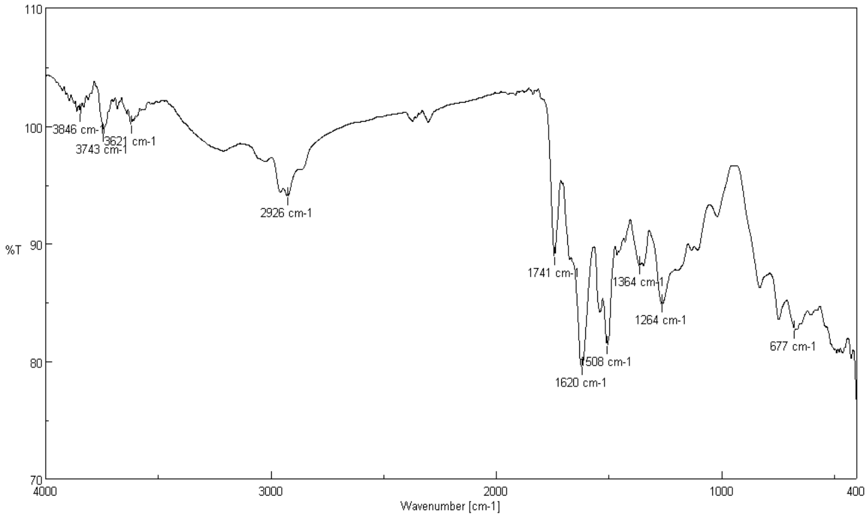


Fig 2c

Fig. 2 : FT-IR Spectra of DP3 (Fig 3a), DP3Cu (Fig 3b) and DP3TiP (Fig 3c)

“In the FT-IR spectra of complexes, the asymmetric and symmetric carbonyl stretching vibration bands are shifted to higher frequency indicating the formation of a linkage between the metal ion and the carbonyl oxygen.[26,28] Other sets of characteristic absorption bands appear in the region 1223 and 1521cm^{-1}. These can be assigned to phenolic C-O and amide N-H stretching vibrations for the free ligands respectively. The phenolic stretching C-O and amide N-H stretching are shifted to a higher frequency upon complexation implying that the phenolic oxygen and amide nitrogen on the dipeptide form coordinate bond with the metal ions.[26,29,30] Conclusive evidence regarding the bonding of the nitrogen and oxygen is provided by the occurrence of bands at 587-515cm^{-1}(M-N) and 507-424cm^{-1}(M-O)[26, 31] [Fig 2] of Schiff base metal complexes of DP2 and DP3.”

“The electronic absorption spectra of the metal complexes were recorded in methanol. The divalent metal complex absorption bands of strong intensity corresponding to C=N chromophore occur at 200-300 nm. These bands are attributed to π- π^* transitions of the extended conjugation system formed by the benzene ring, phenolic oxygen and imino nitrogen confirming the formation of Schiff base metal complexes.[26,32] From the Fig.3, it can be observed that only complexes of copper show peak in this region. The band at, 353, 388, 413 nm have been assigned to n- π* transitions of the C=N chromophore, coupled with the secondary band of the benzene ring.[26,33]”

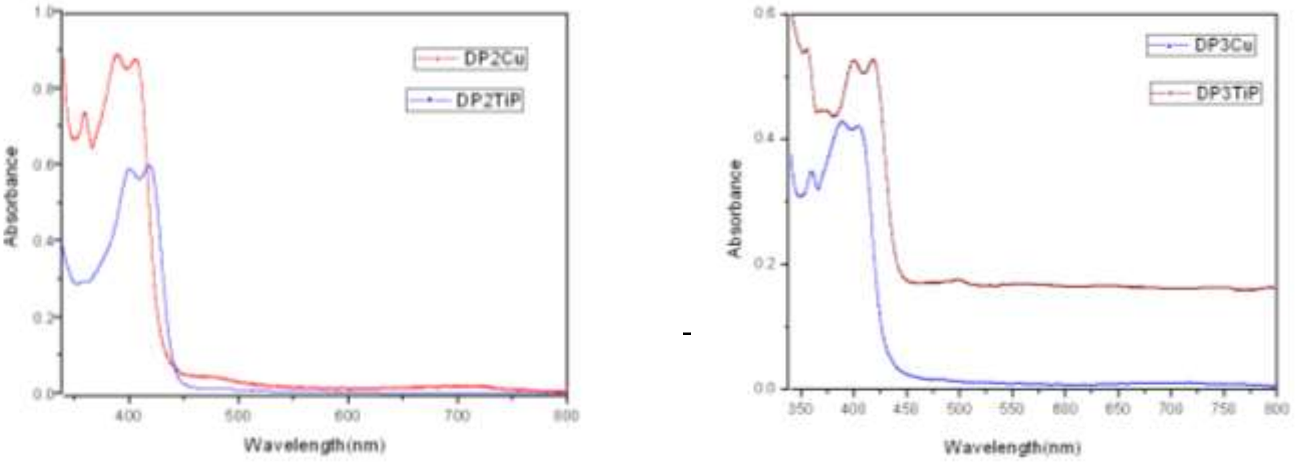


Fig 3. Electronic spectra of Schiff’s base metal complexes of DP2 and DP3

“DRS spectra of the parent Montmorillonite K10, supported copper complex and supported titanium complex catalysts are shown in Fig 4. UV-DRS Spectra of the catalysts are characterized by broad absorption band centered around 400-500 nm in the copper catalysts which are indicated as violet line and band around 260-270 nm and above 300 nm in the case of titanium catalysts marked as green line. The parent Montmorillonite K10 shows no absorption band in this region marked as red line.”

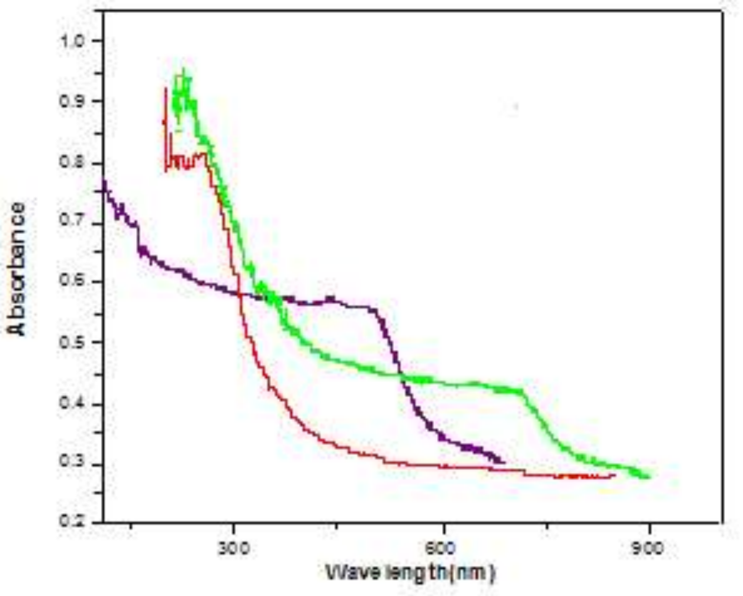


Fig 4. UV-DRS spectra of clay supportedcatalysts derived from DP3

3.4 IR Spectra of DP3Cu supported clay catalyst

FT-IR spectra of K10DP3Cu catalyst, **Fig. 5** showed a weak broad peak in the region 1600 cm^{-1}, characteristic of carbonyl absorption of the dipeptide.

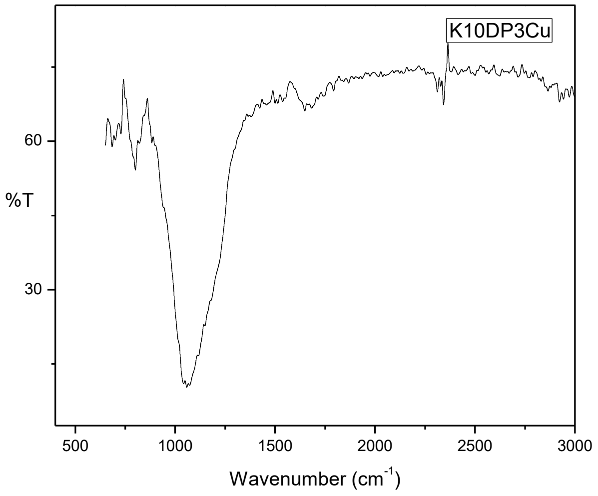


Fig 5.FT-IR spectra of K10DP3Cu

3.5 TG/DTA curve of K10DP3Cu

The thermal stability of the Cu catalyst was studied using thermogravimetry. The catalyst was heated in the temperature range 50-800°C at a heating rate of 10°C/min. Thermogram of the catalyst showed a weight loss around 230°C which might be due to the loss of the organic part. The TG/DTA profile of K10DP3Cu is shown in **Fig.6.**

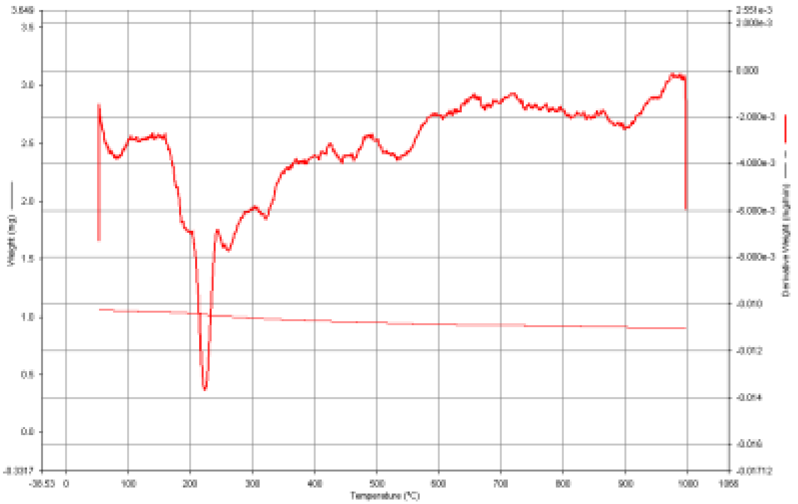


Fig. 6. TG/DTA of K10DP3Cu

3.6 Catalytic activity studies

Various catalyst used for the one pot synthesis of furano [3,2,c] and pyranoquinolines by Aza Diels Alder reaction was compared and the results are given in **table 1**. It is observed that recyclable catalysts for this particular reaction is few and are expensive.

Table 1. Comparitive study various catalysts for the synthesis of pyrano[3,2-c] quionoline by Aza Diels Alder reaction.

Entry	Catalyst	Condition	Time (h)	Yield [%]	Recycle	Ref.
1	Selectfluor TM	CH_3CN	3	92	N	[36]
2	VCl_3	CH_3CN	2.5	90	N	[34]
3	SmI_2	50^{o}C, THF	5	93	N	[35]
4	$GdCl_3$	0^{o}C, THF	30	80	N	[37]
5	$Sm(OTf)_2$	DCM	2.5	90	N	[38]
6	PANI-PTSA	THF	0.2	81	Y	[20]
7	BINOL Bronsted acid catalyst	$CHCl_3$	34	89	N	[39]

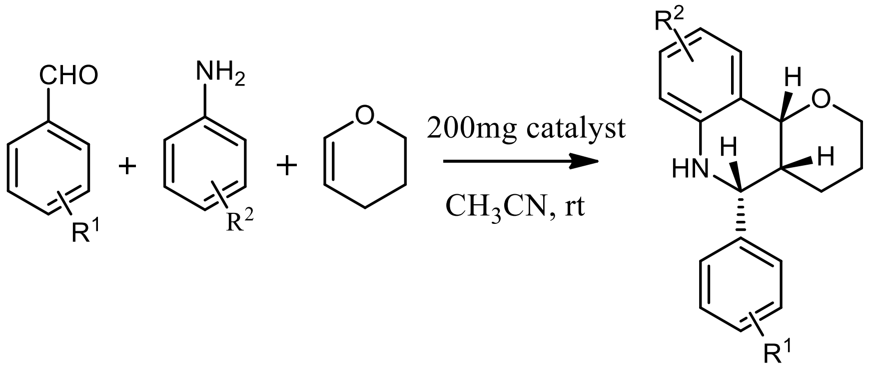
Optimisation of catalyst concentration was done by selecting benzaldehyde, aniline and dihydropyran as substrates. The concentrations such as 50, 100, 150, 200, 250mg were taken and yield of the crude product was noted. It is observed that yield of the product increases as catalyst concentration increases up to 200mg and further increase of concentration has no effect on yield and is considered as the optimal concentration for further studies.

Clay supported, Cu and Ti dipeptide complex catalysts were prepared and characterzied. They were used for the synthesis of furano [3,2,c] and pyranoquinolines by Aza Diels Alder reaction. Benzaldehyde (1mmol), aniline (1mmol), 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (1mmol) were used in acetonitrile (10 mL). 200 mg of the clay supported catalyst was used. The results are summarized in **table 2.** K10DP3Cu showed better result. It was used for further studies.

Table 2. Screening of the catalyst for Aza-Diels Alder reaction

Catalyst	**Metal ion**	**% Yield**
DP2	Cu^{2+}	48
	Ti^{4+}	52
DP3	Cu^{2+}	79
	Ti^{4+}	68

The Aza-Diels Alder reaction was conducted with K10DP3Cu. During the reaction, imines were generated in situ from aldehydes and amines. They reacted easily with dihydropyran to afford pyrano[3,2-c]quinolines in one pot. The pre-formation of imines was not an essential condition. The reaction did not occur in the absence of the catalyst. In the yield of the products, there was no considerable influence of the electronic properties or steric hindrance of the substituents on the aldehydes. Ring-fused [3,2-c] quinolines were obtained in good to excellent yield. High enantioselectivity was observed. General scheme of the reaction is given in **scheme 4.**



Scheme 4. General scheme of Aza-Diels Alder reaction

Different solvents were used in the reaction with Benzaldehyde, aniline and dihydropyran using K10DP3Cu (200 mg) as catalyst. The results are summarized in **table 3**. Acetonitrile was found to be the best solvent. In order to validate the scope of the reaction, it was conducted using different amines and aldehydes. The results are presented in **table 4**. The reaction proceeded in one pot in a three component mode which resulted in the formation of the corresponding pyrano/ furano [3,2-c] quinolines.

Table 3. Effect of solvents on Aza-Diels Alder reaction

Sl.No	Solvent	%Yield of the product
1	$CHCl_3$	76
2	C_2H_5OH	78
3	CH_3OH	82
4	CH_3CN	84
5	H_2O	79

Reaction condition: Benzaldehyde (1mmol), aniline (1 mmol), 2, 3-dihydropyran (1 mmol), 200 mg catalyst, at room temperature for 12h under N_2 atmosphere

Table 4.Aza-Diels Alder reaction of various substrates

Entry	RCHO	RNH_2	Olefin	Yield (%)[a]	M.p°C	ee(%)[b]
1	Benzaldehyde	Aniline	3,4-dihydropyran	79	120	83
2	3-Nitrobenzaldehyde	Aniline	3,4-dihydropyran	68	180	99
3	4-Chlorobenzaldehyde	Aniline	3,4-dihydropyran	71	163	82
4	Benzaldehyde	4-Bromo aniline	3,4-dihydropyran	78	147	81
5	Thiophene-2-carboxaldehyde	Aniline	3,4-dihydropyran	76	145	87
6	4-Methoxybenzaldehyde	Aniline	3,4-dihydropyran	81	-	83
7	Benzaldehyde	Aniline	2,3-dihydrofuran	78	108	81
8	3-Nitrobenzaldehyde	4-Bromo aniline	2,3-dihydrofuran	64	184	89
9	3-Nitrobenzaldehyde	Aniline	2,3-dihydrofuran	62	159	73

Reaction condition: Benzaldehyde (1mmol), aniline (1 mmol), 2, 3-dihydropyran (1 mmol), 200 mg catalyst, at room temperature for 12h under N_2 atmosphere

[a] Isolated yield of purified product

[b] Determined by HPLC with chiral OJ-H column

“The products were characterized by determining the m.p and comparing the IR. ^{1}HNMR spectra were used to establish the cis ring fusion. In the ^{1}HNMR spectra, for the signals at ~5ppm, the coupling constant ($J_{4a,\ 5}$) = 5.2 Hz is small and typical for a guache confirmation of the protons, consistent with all cis-configuration of the hydrogen atoms 4a, 5 and 10b. The coupling constant (J_{4a}, 10_b) in all products (2.2-2.9 Hz) leads to the cis fusion of the pyran-and quinoline rings.”

Recycling studies

When the reaction was completed, the catalyst was filtered, washed several times with acetone, methanol and ethyl acetate. It was dried at 100^{o}C for 1h and reused. There was a slight decrease in the activity of the catalyst after each cycle. The results of recycling studies are summarized in **Fig. 7.** The decrease in yield of product may be ascribed to leaching of bulkier metal complex after each cycle of reaction.

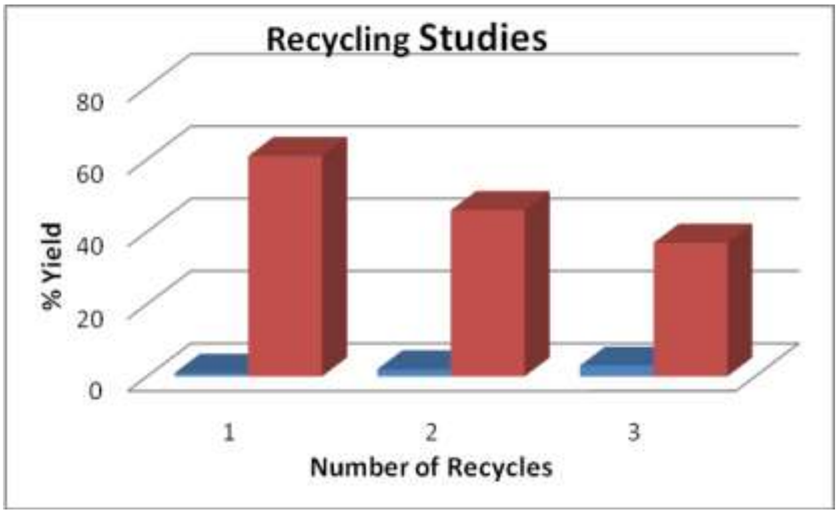


Fig 7. Recycling studies of the catalyst

Reaction condition: Benzaldehyde (1 mmol), aniline (1 mmol), 3, 4-dihydropyran (1 mmol), Catalyst 200 mg, Solvent: acetonitrile (5 mL) Time: 12h, RT

[a]Isolated yield

4. Conclusions

K10 clay supported copper and titanium catalysts were synthesized efficiently with dipeptide ligands obtained from natural amino acids. Their catalytic activity was investigated in Asymmetric Aza Diels alder reaction. The amount of catalyst required was low, good yields and high enantioselectivity were obtained in all the cases studied. The catalyst is recyclable.

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